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GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,  
KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV,  
LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI,  
NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG,  
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FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT,  
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NOVEL PHOSPHORUS-CONTAINING THYROMIMETICS

(57) Abstract: The present invention relates to compounds of phosphonic acid-containing T3 mimetics and monoesters thereof, stereoisomers, pharmaceutically acceptable salts, co-crystals, and prodrugs thereof and pharmaceutically acceptable salts and co-crystals of the prodrugs, as well as their preparation and uses for preventing and/or treating metabolic diseases such as obesity, NASH, hypercholesterolemia and hyperlipidemia, as well as associated conditions such as atherosclerosis, coronary heart disease, impaired glucose tolerance, metabolic syndrome x and diabetes.



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# INTERNATIONAL SEARCH REPORT

International application No  
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## A. CLASSIFICATION OF SUBJECT MATTER

INV. C07F9/02 C07F9/30 C07F9/38 C07F9/40 C07F9/44  
C07F9/572 C07F9/58 C07F9/6571

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, BEILSTEIN Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SCHMITT L ET AL: "Synthesis of Arylalkylmonofluorophosphonates as Myo-Inositol monophosphatase Ligands" TETRAHEDRON LETTERS, ELSEVIER, AMSTERDAM, NL, vol. 39, no. 23, 4 June 1998 (1998-06-04), pages 4009-4012, XP004118798 ISSN: 0040-4039 page 4010; examples 8c,8d,9c,9d	1
X	page 1, paragraph 1	48
X	DATABASE BEILSTEIN [Online] BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; XP002403230 retrieved from Xfire Database accession no. BRN 7260579, BRN 7260578, BRN 7227886, BRN 7222862 abstract -/--	1

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

### \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- \*G\* document member of the same patent family

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## INTERNATIONAL SEARCH REPORT

International application No  
PCT/US2006/020607

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	& DRESCHER, M. ET AL.: TETRAHEDRON, vol. 51, no. 17, 1995, pages 4399-4946, ----- DATABASE BEILSTEIN [Online] BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; XP002403231 retrieved from XFIRE Database accession no. BRN 7505261 abstract & BERGIN, C. ET AL.: J. CHEM. SOC CHEM. COMMUN., vol. 10, 1996, pages 1155-1156, -----	1
X	DATABASE BEILSTEIN [Online] BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; XP002403232 retrieved from XFIRE Database accession no. BRN 6636403, BRN 6636402 abstract & JACQUIER, R. ET AL.: PHOSPHORUS, SULFUR, SILICON, RELAT. ELEM., vol. 81, no. 1-4, 1993, pages 83-88, -----	1
X	WO 03/061567 A2 (MERCK & CO., INC., USA) 31 July 2003 (2003-07-31) page 118; example 5	1
X	page 11, lines 11, 31; page 31, lines 7, 27claim 14	48
P,X	----- DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; ERION, MARK D. ET AL: "Preparation of phosphonic acid-containing liver-selective thyromimetics effective against metabolic diseases" XP002403233 retrieved from STN Database accession no. 2005:490263 abstract	43-72
P,X	-& WO 2005/051298 A2 (METABASIS THERAPEUTICS, INC., USA) 9 June 2005 (2005-06-09)	43-72
X	----- WO 99/00353 A1 (KARO BIO AB, SWED.) 7 January 1999 (1999-01-07)  claim 11; examples 14,15 claim 20 claim 21 claim 22  ----- -/--	43-46, 48,62, 63,66

# INTERNATIONAL SEARCH REPORT

International application No  
PCT/US2006/020607

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 3 357 887 A (FRED KAGAN ET AL) 12 December 1967 (1967-12-12) the whole document -----	1
A	LIU, YE ET AL.: "Thyroid Receptor Ligands" J. MED. CHEM, no. 46, 2003, pages 1580-1588, XP002403225 Scheme 1, "Chemistry" and "Effects of the Ligands on Thyroid Hormone Receptors"figure 1; table 1 -----	1
A	WO 02/11666 A2 (DPHARM LTD [IL]; KOZAK ALEXANDER [IL]; VINNIKOVA MARINA [IL]; POLYAK M) 14 February 2002 (2002-02-14) page 4 -----	1
A	ING H R ET AL: "PROGRESS IN DRUG RESEARCH FORTSCHRITTE DER ARZNEIMITTELFORSCHUNG PROGRES DES RECHERCHES PHAMACEUTIQUES VOL.7" PROGRESS IN DRUG RESEARCH - FORTSCHRITTE DER ARZNEIMITTELFORSCHUNG - PROGRES DES RECHERCHES PHARMACEUTIQUES, BIRKHAUSER VERLAG, BASEL, CH, vol. 7, 1964, pages 306-309, XP002195729 ISSN: 0071-786X the whole document -----	43
A	THORNBUR C W: "ISOSTERISM AND MOLECULAR MODIFICATION IN DRUG DESIGN" CHEMICAL SOCIETY REVIEWS, CHEMICAL SOCIETY, LONDON, GB, vol. 8, no. 4, 1979, pages 563-580, XP000953019 ISSN: 0306-0012 table 1 -----	43
A	HOLY A: "PHOSPHONOMETHOXYALKYL ANALOGS OF NUCLEOTIDES" CURRENT PHARMACEUTICAL DESIGN, BENTHAM SCIENCE PUBLISHERS, SCHIPHOL, NL, vol. 9, December 2003 (2003-12), pages 2567-2592, XP008058387 ISSN: 1381-6128 chart 5. page 2577 -----	44,46

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210****Continuation of Box II.1**

Although claims 54-72 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds

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**Continuation of Box II.2****Claims Nos.:**

The high number of provisos in independent claim is objectionable under Article 6 PCT according to which the claims should define the matter for which protection is sought and should be clear and concise. The instrument of a disclaimer may only be used in an exceptional case. Owing to the exceptional nature of a disclaimer a high number of disclaimers cannot be accepted.

The present application contains many independent claims. There is no clear distinction between the independent claims because of overlapping scope. There are so many claims, and they are drafted in such a way that the claims as a whole are not in compliance with the provisions of clarity and conciseness of Article 6 PCT, as it is particularly burdensome for a skilled person to establish the subject-matter for which protection is sought. The non-compliance with the substantive provisions is to such an extent, that the search was performed taking into consideration the non-compliance in determining the extent of the search (PCT Guidelines 9.19 and 9.25).

The search was based on the examples and on the subject-matter according to claim 1 for R52 = H.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

## INTERNATIONAL SEARCH REPORT

International application No.  
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### Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Although claims 54-72 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds
2. ☒ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

see annex

#### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1, partially:16, 18-42, 47-72

compounds of formula VIII according to claim 1,  
pharmaceutical compositions comprising such compound of  
formula VIII, methods including a therapy using such  
compound of formula VIII

1.1. claims: 43, partially: 47-72

compounds according to claim 43, pharmaceutical compositions  
comprising these compounds and methods including a therapy  
using these compounds

1.2. claims: 44, partially 47-72

compounds according to claim 44, pharmaceutical compositions  
comprising these compounds and methods including a therapy  
using these compounds

1.3. claims: 45, partially: 47-72

compounds according to claim 45, pharmaceutical compositions  
comprising these compounds and methods including a therapy  
using these compounds

1.4. claims: 46, partially: 47-72

compounds according to claim 46, pharmaceutical compositions  
comprising these compounds and methods including a therapy  
using these compounds

2. claims: 2, partially: 17, 20-42,47-72

compounds of formula VIII according to claim 2,  
pharmaceutical compositions comprising such compound of  
formula VIII, methods including a therapy using such  
compound of formula VIII

3. claims: 3, partially: 17-29, 34-42, 47-72

compounds of formula VIII according to claim 3,  
pharmaceutical compositions comprising such compound of  
formula VIII, methods including a therapy using such  
compound of formula VIII

4. claims: 4, partially:17-25, 28-42, 47-72

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

compounds of formula VIII according to claim 4,  
pharmaceutical compositions comprising such compound of  
formula VIII, methods including a therapy using such  
compound of formula VIII

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5. claims: 5, partially:8-10, 16, 20-25, 30-42, 47-72

compounds of formula II according to claim 5, pharmaceutical  
compositions comprising such compound of formula II,  
methods including a therapy using such compound of formula  
II

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6. claims: 6, partially:8-10, 17, 20-25, 30-42,47-72

compounds of formula II according to claim 6, pharmaceutical  
compositions comprising such compound of formula II,  
methods including a therapy using such compound of formula  
II

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7. claims: 7, partially: 8-10, 17, 20-25, 34-42,47-72

compounds of formula II according to claim 7, pharmaceutical  
compositions comprising such compound of formula II,  
methods including a therapy using such compound of formula  
II

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8. claims: 11, partially:15,16, 18-25, 30-42, 47-72

compounds of formula III according to claim 11,  
pharmaceutical compositions comprising such compound of  
formula II, methods including a therapy using such  
compound of formula III

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9. claims: 12, partially:15, 17, 20-25, 30-42,47-72

compounds of formula III according to claim 12,  
pharmaceutical compositions comprising such compound of  
formula III, methods including a therapy using such  
compound of formula III

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10. claims: 13, partially:15, 17-25, 30-42, 47-72

compounds of formula III according to claim 13,  
pharmaceutical compositions comprising such compound of  
formula III, methods including a therapy using such  
compound of formula III

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11. claims: 14, partially:15, 17-25, 34-42, 47-72